

REVIEW ARTICLE

The bidirectional mechanisms of anxiety, depression, and malnutrition in patients with gastrointestinal tumors

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This study summarized the current state of malnutrition and anxiety–depression in patients with gastrointestinal malignancies and determined the relationship between them. Many of these patients suffered from malnutrition at various stages of their illness and treatment, which often resulted in a poor prognosis. Additionally, the rate of surgical complications was reportedly high, which had a significant negative impact on patients' quality of life. According to a survey, mental illnesses such as anxiety and depression could interfere with the hypothalamic–pituitary–adrenal (HPA) axis, which could hinder the absorption and utilization of nutrients, resulting in nutritional deficiencies and promoting the occurrence of malnutrition-related symptoms. Moreover, adverse psychological problems were among the most easily overlooked complications in patients with gastrointestinal tumors. The data collected were focused on the two-way mechanism of action between gastrointestinal tumors and anxiety–depression, as well as the newly introduced psychological intervention strategies that were anticipated to serve as the theoretical foundation for future rehabilitation techniques and mental health enhancement strategies for patients with gastrointestinal tumors.

Keywords: malnutrition; nutritional deficiencies; anxiety; depression; gastrointestinal cancers.

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Introduction

Gastrointestinal cancers constitute a quarter of new cancer cases worldwide, and one-third of mortality is associated with gastrointestinal malignancies [1]. According to projections, East Asia's gastrointestinal tumor incidence and associated mortality rates are expected to increase by 58.00% and 73.00%, respectively, over the next 20 years. Cancers of the digestive system, a multiorgan system that includes the esophagus, stomach, small intestine, and large intestine and is essential for barrier immunity and nutritional absorption, accounts for 41.60%

of new cancer diagnoses and 49.30% of cancer deaths in China [2, 3]. The development of malignant tumors is influenced by a complex interaction of variables such as mutations, certain types of sensitive cells, and inflammation generated by the microbiota [4]. Research has shown that *Helicobacter pylori* infection is linked to stomach cancer [5]. This infection is associated with both acute and chronic infiltration of inflammatory cells into gastric mucosa, which changes the normally acid-secreting mucosa into metaplastic epithelium including intestinal and pyloric metaplasia that expresses spasmolytic polypeptides, which in turn leads to gastric

cancer [6]. In contrast, colorectal cancer is a serious condition caused by the interaction of several risk factors including smoking, excessive alcohol use, the consumption of large quantities of red and processed meats, inflammatory bowel disease, obesity, diabetes, age, sex, and genetic family history. Furthermore, according to the most current data, *Helicobacter pylori* infection is one of the factors that contributes to colorectal cancer development [7]. Although colorectal cancer screening has advanced significantly, the disease burden is still substantial, and the prognosis for other gastrointestinal malignancies is generally dismal [8]. Despite improvements in cancer lesion technology and increased detection rates in recent years, gastrointestinal cancers sometimes manifest late in the progression of the disease. Those with advanced malignancies, however, have a poor prognosis [9].

Malnutrition results from high metabolism, inflammation, and other tumor-related conditions. In fact, nutritional status is the primary determinant of how the disease progresses and how long a patient lives [10]. Twenty percent of cancer-related deaths are caused by malnutrition rather than the illness itself, meaning that one person out of every five who dies from the disease does so because of malnutrition. Severe malnutrition is responsible for 32% early fatalities in low- and middle-income countries, but it accounts for only 40% of early deaths in wealthier upper-middle-income countries [11]. Malnutrition is the highest among those with gastrointestinal malignancies, primarily those having gastric, colorectal, and esophageal cancers. Malnourished patients account for 79% of all esophageal cancer patients [12]. Conversely, in patients with gastric cancer, the percentage of malnourished patients is reported to be between 65.00% to 85.00% [13]. The number of patients with malnutrition can reach 80% in the final stages of gastrointestinal cancer [14]. Studies have demonstrated that malnutrition is a risk factor for lower survival and early cancer recurrence in cancer patients [15].

Signs of malnutrition in patients with gastrointestinal malignancies

Compared with non-malnourished patients, malnourished individuals with cancer are reported to have greater fatigue scores ($P < 0.001$), decreased appetites ($P < 0.001$), and increased nausea and vomiting ($P = 0.002$) [16]. Sepsis with adynamic features, hypothermia, leukopenia, somnolence, wound healing disincentives, and pus production may be observed in patients with severe malnutrition, eventually, these patients may die slowly [17]. Individuals with cancer of the digestive system are more likely to experience nutritional deficiencies due to a lack of vitamins, minerals, and digestive fluids [18]. Prior to, during, and following surgery for a gastrointestinal tumor, patients are more likely to experience vitamin and other dietary deficits. According to a study that examined the 25-OH Vit D₃ levels of 293 patients who had undergone esophageal or gastric cancer surgery or gastrectomy, these patients had significantly lower levels than that in the control group ($P < 0.001$) with an average of 27.51 ng/dL, while 30–100 ng/dL was the normal range [19]. The cardiovascular and immunological systems both depend on vitamin D. The cardiovascular system is represented by arterial wall cells, cardiomyocytes, and immune cells, all of which contain vitamin D [20]. Moreover, vitamin D deficiency may also be linked to orthostatic hypotension [21]. For this reason, if arrhythmia, dizziness or confusion occurs, vitamin D deficiency should be considered. According to emerging data, vitamin B₁₂ might involve a major position in various parts of human health including the composition and function of the gastrointestinal microbiota. A scarcity of vitamin B₁₂ can adversely affect cellular proliferation, hemoglobin synthesis, the stability of DNA sequences, and neuronal function [22]. Vitamin B₁₂ is needed to initiate the methionine and folate cycle processes carried out by the cofactors of enzymes. Kennedy emphasized the idea that all B vitamins work together in the biological processes of homocysteine metabolism and DNA methylation

[23]. Consequently, these metabolic pathways may be restricted by a lack of one or more of these nutrients, which could result in the buildup of homocysteine [24]. High homocysteine levels are a disorder that affects approximately 30% of people who suffer from depression. Therefore, it makes sense that taking B vitamins, which lower homocysteine levels, could improve mood. Furthermore, pernicious anemia may result from severe vitamin B12 deficiency [25]. The body uses iron in many biological processes including the acquisition of oxygen, the synthesis of DNA, the production of energy, and cellular respiration [26]. In patients with gastrointestinal tumors, iron absorption is frequently hindered by the surgical removal of a portion of the digestive tract. The origin of the metal generally from red blood cells or proliferative cells, the mechanisms of transportation and circulation through intestinal cells or splenic macrophages, and storage in liver cells all contribute to the well-coordinated acquisition of iron [27]. If iron deficiency is not treated, anemia will occur. Additionally, Stewart and Hirani looked at almost 2,000 older people and proposed that depressive symptoms were linked to lower-than-normal hemoglobin, ferritin, and transferrin levels [28].

Current status of depression and psychological anxiety in patients with malnutrition and gastrointestinal tumors

In addition to physical stress, patients with stomach cancer experience psychological problems such as anxiety and sadness [29]. Additionally, in the cancer group, individuals with mental illnesses have lower expectations for treatment [30]. New-onset mental health diagnoses after a cancer diagnosis are also associated with a higher risk of death in people without a history of mental disease [18]. Nearly all cancer patients suffer some level of discomfort at different phases of the disease, even in the absence of a recognized mental health diagnosis, and a higher level of distress can have a substantial detrimental effect on survival [19]. Patients with gastrointestinal

malignancies may experience anxiety and depression at rates as high as 47.2% and 57%, respectively. In addition to causing changes in the mental health of cancer patients, this emotional discomfort is a significant factor in treatment compliance and a major determinant of overall quality of life [31]. Negative emotional states directly increase the mortality rate and significantly impede the course of treatment for patients with gastrointestinal cancers [32, 33]. To develop effective interventions and promote the recovery of patients with gastrointestinal cancer, investigating the relationships between nutritional status, psychological symptoms, and their involvement in the outcomes of these patients is crucial. In this study, the reciprocal impacts of malnutrition and unfavorable psychological states on the etiology of gastrointestinal cancers were investigated. A meta-analysis of 44 studies with over 50,000 long-term cancer survivors revealed that the prevalence of anxiety ranged from 3.40% to 43.00% with a total prevalence of 21.00% and the level of anxiety being even higher after the diagnosis when patients were dealing with the initial shock and problems related to the diagnosis [34]. A systematic review of 210 studies reported that the average rate of depression in all forms of cancer was 21.20% [35]. In patients with colorectal cancer (CRC), the reported rates of anxiety and depression ranged from 1.0% to 47.2% and from 1.6% to 57%, respectively. With respect to the prevalence of anxiety and depression in stomach cancer patients, mild anxiety was reported by 15.9%, symptomatic anxiety by 32%, and mild and symptomatic depression by 25% and 28%, respectively [36]. Anxiety symptoms are 1.98 times more prevalent in malnourished patients than in the general population [37]. A higher level of psychological distress, which is typified by more severe fatigue, insomnia, anxiety, and depression, is typically experienced by those who are undernourished, experiencing weight loss, and exhibiting other malnutrition symptoms. This, in turn, increases the likelihood that the disease will worsen [38]. Research has shown that depression is associated with reduced food intake, weight loss, and

malnutrition [39].

Mechanisms of depression and anxiety exacerbating malnutrition

Most cancer survivors adjust to life effectively after cancer, but anxiety, sadness, posttraumatic stress disorder, and cancer-related dread might affect them [40]. Although it is rarely given proper care, cancer is a disease that is frequently linked to depressive and anxious emotional states [41]. Inadequate control of emotions such as depression and anxiety may cause the release of certain hormones into the body through the β 2-adrenergic receptor and epithelial-mesenchymal transition (EMT) pathways [42]. Clinically speaking, anxiety and depressive episodes may be linked to disruption of the hypothalamic–pituitary–adrenal (HPA) axis, a critical component of the neuroendocrine system that controls the body's hormone balance and stress response. Variations in stress hormone and catabolic hormone levels caused by HPA axis dysfunction interfere with the release of gastrointestinal hormones including corticotropin-releasing hormone, adrenocorticotrophic hormone, and cortisol, which leads to abnormal gastrointestinal motility and digestion [43], and in turn affects how well patients absorb nutrients. Zhu *et al.* conducted a study at West China Hospital (Chengdu, Sichuan, China) to assess the impact of psychology and diet on 525 cancer patients and reported a strong correlation between higher levels of psychological stress and higher nutritional risk scores derived from the Patient-Generated Subjective Global Assessment (PG-SGA) ($r = 0.148$, $P < 0.001$) and Nutrition Risk Screening 2002 (NRS2002) ($r = 0.142$, $P < 0.001$). The findings of the correlation analysis suggested that psychological levels and nutritional status might be positively correlated ($P < 0.001$) [44]. Previous research has demonstrated that elevated levels of stress-related proinflammatory cytokines such as C-reactive protein (CRP), IL-1, IL-6, and TNF might result in the development of anxiety and depressive symptoms [45]. A lack of appetite,

inadvertent weight loss, and the subsequent development of malnutrition are also associated with serotonin depletion, which has been identified as a common mechanism for mood and appetite disorders. Elevated levels of inflammatory mediators such as C-reactive protein may put cancer patients at increased risk for depression [46]. Renna *et al.* emphasized that nearly one-third of colon cancer patients who reported clinically significant depression symptoms also had high CRP levels defined as > 3 mg/L. Owing to some biological mechanisms, stress could be increased to a degree that cancer patients could not cope with, which might lead to persistent depressive symptoms following treatment [35].

The intervention programs dealing with psychological problems

Depressive symptoms can be reduced by nutritional therapies aimed at improving food quality [47]. Many items, like those in the "Mediterranean diet," such as nuts, lean meats, fish, legumes, and leafy green vegetables, are thought to enhance "dietary quality" and mood [48]. Recent advances in the study of the human microbiome have shown a clear correlation between the start of anxiety and depression in humans and gut ecological dysbiosis (GD) or gut dysbiosis [38, 39, 49, 50]. Through neural, immunological, and metabolic pathways, the gut microbiota communicates with the brain either directly through the vagus nerve or indirectly through metabolites derived from the gut and microbiota, as well as gut hormones and endocrine peptides that include peptide YY, pancreatic polypeptide, neuropeptide Y, cholecystokinin, corticotropin-releasing factor, glucagon-like peptide, oxytocin, and ghrelin. Because of this communication, promoting varied and healthy gut microbiota (GM) by fecal transplantation (FMT), probiotics, prebiotics, and synbiotics is considered a crucial first step toward mental well-being. According to some research findings, restoring the function of the HPA axis and the gut microbiota may have antidepressant

effects. Probiotics that target *Lactobacillus rhamnosus* (*L. rhamnosus*, bb-1) have been shown to lower plasma corticosterone levels and reduce the expression of aminobutyric acid (GABA) A2 mRNA in the prefrontal cortex and amygdala [51]. However, supplementation with *Lactobacillus* strains also increased hippocampal Brain-Derived Neurotrophic Factor (BDNF) and prefrontal and frontal cortex serotonin levels in mice. As a result, the mice were less stressed and did not exhibit depressive or anxious behaviors [52]. Psychoeducational therapy (PE) [40], mindfulness therapy [53], cognitive-behavioral therapy (CBT), relaxation therapy [41], reminiscence therapy [54], art therapy [42], and other forms of treatment have been shown to be effective in objectively lowering anxiety and depression in patients with gastrointestinal cancer compared with standard practices. This association has not yet been supported by data. However, there is limited evidence from studies that psychological treatments may be beneficial for patients with gastrointestinal cancer. Future studies should prioritize larger sample sizes to make the findings more credible and scientific [43].

Conclusion

Patients with gastrointestinal malignancies are particularly vulnerable to malnutrition, which frequently leads to nutritional deficiencies among cancer types [48]. Poor nutritional conditions have been linked to a decline in mental health, and postoperative patients with gastrointestinal malignancies who are unable to maintain a normal diet are particularly vulnerable to malnutrition and associated problems [55]. Moreover, malnutrition can be exacerbated by mental health conditions such as sadness and anxiety [43]. The reciprocal impacts of anxiety, sadness, and nutritional status in patients with gastrointestinal malignancies must also be considered. The processes behind the associations between malnutrition and anxiety and depression in individuals with gastrointestinal malignancies have not yet been

specifically addressed in any research. To guide interventions that can improve the postoperative recovery of patients with gastrointestinal malignancies, further studies on these pathways are desperately needed. These interventions can help patients improve quality of life, lower postoperative mortality, and improve disease prognosis.

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